



CELEBREX, AND ANTI-CANCER ACTIVITY

Malignant melanoma is the most aggressive form of skin cancer by far, and metastatic melanoma is one of the most aggressive of all cancers with extremely short survivals. Most of us know that it arises from moles or freckles that we all have. We are aware that exposure to the sun dramatically increases the risk to develop melanoma. If melanoma has not spread to nearby lymph glands, or to any distant site such as lungs, liver, brain, bones, etc., and if it is less than 1.5 mm thick, the chances for cure are very good -- over 80% plus. But if melanoma spreads to any distant site, the median survival is approximately seven months. If it spreads to the brain, survival is only about three months.

When I trained as an oncologist in the 1970's, the most effective chemotherapy medicine for metastatic melanoma was DTIC, although it only had a response rate of about 20%, and responses averaging only three to six months. As of 2007, no drug has a higher response rate in melanoma than DTIC. Oncologists consider metastatic melanoma to be one of the most difficult of all cancers to control and to put into remission. Metastatic melanoma is resistant to almost all types of chemotherapy.

An article appeared in the journal, *Cancer Investigation*, 24:740-746, 2006 by Dr. Kenneth Wilson from the British Columbia Cancer Agency in Victoria, British Columbia. It reported on some clinical responses in patients with metastatic malignant melanoma who were treated with Celebrex as a single agent.

One case report describes a 57-year-old male who had surgery on his right arm for a melanoma lesion in 1995. It had already spread to several lymph glands in his armpit area, and these glands were also removed. He did well until June of 1998, when a CT scan demonstrated multiple pulmonary metastases, which progressed in spite of cancer vaccine, through March of 2000. When melanoma spreads to the lungs, it is not lung cancer, but melanoma cells in the lung. On April 1, 2000, this patient read a Canadian newspaper, *The National Post*, that had an article describing the antiangiogenic properties of Celebrex. Shortly thereafter, he had an episode of gout and, at his request, his family physician prescribed Celebrex, 200 mg per

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day, for him to help the gout attack and, hopefully, to help his metastatic melanoma, too. A follow-up chest x-ray in July 2000 showed regression of his lung metastases. Subsequent CT scans and chest x-rays have confirmed this extraordinary complete remission. His remission had been sustained through May 2006, when this article was submitted for publication. As of that date, his CT scan of the lung and chest x-ray remained normal without any islands of melanoma cells visible anywhere. This means he was in a complete clinical remission without any evidence of metastatic disease more than six years after his lung metastases were first identified. His only treatment had been Celebrex.

A second case report was that of a 53-year-old male who had melanoma on his chest wall in May of 1995. In August of 2001, a nodule from his anterior abdominal wall was removed, which showed metastatic melanoma. In February 2003, a chest x-ray identified multiple metastatic spots, each of which grew up to approximately 2 cm in diameter by March 2003. He was started on Celebrex alone, and in June of 2003, a chest x-ray showed improvement. In November 2003, the chest x-ray was read as no active abnormality identified on chest film. This is also an example of a complete clinical remission, with no evidence of disease. This does not mean that the patient is cured. It means that no disease can be found on exam, and that all x-rays and scans are normal. No scan is able to exclude microscopic disease. That is why we say remission, not cure.

A third case report involved a 52-year-old female who in 1996 was found to have melanoma in the retina of her left eye. She had her left eye removed to try to cure this form of melanoma. In October 2003, a CT scan identified multiple liver metastases as large as 3 cm in diameter, as well as metastases to kidney, lung, and adrenal gland. Patients who have metastatic melanoma that has spread to their brain have the poorest survival, averaging only about three months. The next worst prognostic category are patients who have metastatic disease to the liver, and their average survival is not much better than patients with brain metastases (about three to five months). In November of 2003, this patient was started on Celebrex. In November 2004, a CT scan confirmed significant regression in her liver metastasis; although subsequent to that, she developed progression in the metastasis involving her right kidney. However, the fact that her liver metastases were controlled for more than one year using Celebrex alone is the third example of what must be acknowledged as miraculous responses.

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These three melanoma responses were in a series of 27 patients. For the entire series of 27 patients, the overall average survival from the time of first incurable metastasis was 31.9 months. Remember that the expected survival for these patients statistically is only six to seven months. Two of these patients had clinical complete remissions of their metastatic disease. They both remained in continuous complete remission more than 58 and 18 months from the time treatment with Celebrex first began. If someone had asked me if I thought that these types of responses were possible with any medicine, I would have responded, "No." If I were asked if Celebrex alone could ever result in these remissions, I would state with absolute (wrong) certainty that it would be impossible, and I would further emphasize that if anyone told you otherwise, you should not believe them because they almost certainly had to be lying. This would be an example of one of my favorite quotes: "Everyone is entitled to their own (wrong) opinion." Unfortunately, I would be the one with the wrong opinion. If Celebrex can do this in a disease that is considered refractory to almost all therapies, what kind of responses could occur in patients who have prostate cancer?

What follows is what I consider to be another miraculous response using Celebrex, this time as a single agent to treat a patient with metastatic, hormone refractory prostate cancer (HRPC). In the August 2005 Mayo Clinic Proceeding (8:1100-1101), there is a letter to the editor by Guru Sonpavde that should convince all of us about the potential benefit using Celebrex for patients with HRPC. This case report describes a 53-year-old man, who presented with urinary discomfort, low back pain, and a bone scan showing widespread metastatic disease. His PSA was 522, and Gleason score 9. He was started on Lupron and Casodex, and after six months of therapy, his PSA dropped to 4. However, three months later, his PSA rose to 22, and then to 37. This means that he had metastatic HRPC. His Casodex was discontinued. Twelve months after initiating treatment, his PSA was 55, and he was started on ketoconazole/hydrocortisone. In spite of this, his PSA rose to 80 one month later, and he developed worsening low back pain. He refused to be treated with chemotherapy. Because of his bone pain, he was started on Celebrex, 200 mg per day. Within days, he had clinical improvement, with resolution of his back pain. Two months after starting Celebrex, his PSA dropped to 5.48. That represented his nadir PSA value, but this was a 99% reduction in PSA compared to his PSA reading when he first presented.

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Four months after starting Celebrex, his PSA was 11.5, and his dose was increased to 200 mg twice each day. His PSA dropped to 10.4. Six months after starting Celebrex, his PSA was 22; it was almost 80 when he started Celebrex. Thus, in a patient with extremely aggressive, metastatic HRPC, who was treated only with Celebrex as a single agent, his PSA was more than 70% lower after six months of Celebrex treatment than prior to starting Celebrex. Remember that one of Dr. Bob's major "Laws of Oncology" states that essentially any medicine that works well in advanced disease, virtually always works much, much better when used in earlier stages of disease. I do not know of any exceptions to this "Law."

This case report is the most dramatic response to Celebrex as a single agent to control metastatic HRPC that I have ever heard about or seen. Remember that Celebrex is just one of the ingredients in my antiangiogenic cocktail (AAC). I believe that when you treat prostate cancer with only a single agent, it is fairly easy for the cancer cells to mutate and become resistant to it. Using the various ingredients in my AAC is a way to help avoid the development of resistance. Some of the other medicines in my AAC include Leukine, thalidomide and/or Revlimid (for an excellent summary of these antiangiogenic medicines, please go to my website, compassionateoncology.org, and download the paper, "LEUKINE (GM-CSF) and REVLIMID, the Second Generation THALIDOMIDE Product," for free. Other agents in my antiangiogenic cocktail include Proscar (occasionally Avodart), Aredia (and much less often Zometa), low-molecular weight heparin (blood thinner), Avastin, targeted therapies (such as Nexavar, Sutent), very low-dose alpha interferon, and metronomic schedule of cyclophosphamide. This list changes very often, and patients are only treated with some of them at any one time; never all of them at the same time.

At the American Urologic Association Meeting, May 21, 2005, Abstract Number 828 reports on the use of Celebrex and its effect on prostate cancer. The authors are Derksen, J. Eric, et al. Forty patients who had rising PSA's following radiation therapy (#8), or radical prostatectomy (#32), were treated with Celebrex, 200 mg twice per day (12 patients), or 400 mg twice per day (28 patients). Most patients have an 18 month follow-up. Thirty-six of 40 patients (90%) had an inhibitory effect on PSA after three months. Eleven out of 40 had an actual decline in PSA; eight out of 40 had stabilization. Of the remaining 21 patients, 17 of them showed a slowing of their PSA doubling time (DT) after starting Celebrex by an average of

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4.5-fold, compared to pre-Celebrex. If the PSA doubling time was four months before Celebrex, it was 18 months on Celebrex. Only four patients failed to demonstrate a slowing of the PSA doubling time at three months follow-up, but three of these four eventually did show a slowing of PSA doubling time from .2-fold to 4.0-fold at the 12 month follow-up. This suggested that they needed a longer period of treatment before benefitting from Celebrex.

The short-term responses seen initially at three months continued at six, 12, and 18 months, which were the study mandated PSA follow-up measurement points. The improved slower PSA doubling times persisted at all time points measured. Only two of the initial 40 patients failed to improve their PSA. These new results represented an expanded study previously reported and described in prior versions of my COX-2 paper.

Abstract No. 4593, by Pruthi, R., et al., in the Proceedings of the American Society of Clinical Oncology, Volume 23; 2004, reports on 24 patients who had serially rising PSA levels following radical prostatectomy (20 patients) or radiation therapy (four patients). Patients were treated with Celebrex, either 200 mg twice each day or 400 mg twice each day. Twenty-two of 24 (92%) had a favorable PSA response. Eight out of 24 had an absolute decline in PSA; three additional patients with rising PSA's before Celebrex had their levels stabilize after starting Celebrex. Of the remaining 13 patients, 11 had slowing of their PSA doubling time, with the average doubling time slowing 4.5-fold compared to pretreatment. Responses at three months continued at six and 12 months. There was a significant shift for patients with rapid baseline PSA doubling times to slower or stable doubling times after starting Celebrex. This benefit persisted at each time point measured. Testosterone levels did not change.

The authors concluded that COX-2 inhibitors help control rising PSA's in patients with biochemical progression after radiation therapy or radical prostatectomy. These results suggest COX-2 inhibitors may delay prostate cancer disease progression.

Following radical prostatectomy, your PSA is expected to be less than 0.02 within one month of surgery. If your PSA is higher and rising, it means that surgery failed to cure you. Unfortunately, each year, more than 60,000 American men have rising PSA's following radical prostatectomy, radiation

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therapy, or seeds; 60,000 men each year who are not cured in spite of their radical local therapy. These 60,000 men, unfortunately, have been exposed to the all too often permanent, life-altering side effects from their treatments including the risk of impotence, urinary or fecal incontinence, urinary irritative symptoms, urinary frequency, and other far too unpleasant side effects.

Urologists and radiation therapists have a difficult time admitting that radical prostatectomy did not cure you. The urological literature has 55 different PSA definitions of "cure." Even worse, urologists and radiation therapists do not label patients with a rising PSA after radical prostatectomy or radiation therapy as patients who failed to be cured by their radical local therapy. They call them "biochemical failures" because their PSA levels are rising. They will not use the term "failure" until the patient has an abnormal bone scan, another abnormal scan, or evidence of a local recurrence. It usually takes anywhere from several years to more than five plus years before the source or sources for their rising PSA can be identified. This means that biochemical failure (a rising PSA) precedes clinical failure (the discovery of metastases or a local recurrence) by many years. By creating this biochemical failure category, urologists and radiation therapists are able to pretend that their success rates are higher than they are. By definition, if a patient has a progressively rising PSA following local therapy, he was not cured by that therapy. The radical local therapy failed to cure him. Instead of admitting this, they seem to want to imply that if this patient dies of some unrelated condition (like a heart attack or stroke, etc.) with a rising PSA but normal scans, then his therapy was successful and did not fail this patient. This is nonsense, dishonest, misleading, absurd, and an insult to our intelligence. This patient might have lived just as long without the radical prostatectomy or radiation therapy, and would not have been exposed to all of the side effects and toxicities of the failed local therapy. Checking the medical literature, one can find 99 different definitions of cure following radiation therapy based on PSA levels. By changing the definition of cure, you can dramatically improve your reported "successful outcomes." Hiding behind a term like biochemical failure rather than using true failure makes it much more difficult for a recently diagnosed prostate cancer patient to try to become educated about treatment options and honest outcomes.

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Radical prostatectomy removes all prostate tissue, malignant and benign. Dr. Bob believes that a rising PSA after radical prostatectomy is almost always coming from occult, metastatic prostate cancer cells somewhere in the body (almost always from bones). Other sites such as lymph nodes may also harbor occult prostate cancer metastases. Compassionate Oncology believes that isolated local recurrences are extremely uncommon. We feel that men with a local recurrence invariably also have metastatic prostate cancer cells in sites distant from the prostate, especially in bones. Since studies have found that Celebrex had a beneficial effect on PSA levels for patients with rising PSA's after radical prostatectomy or radiation therapy, and since radical prostatectomy removes all prostate tissue, it seems obvious that Celebrex must be having a positive beneficial effect against prostate cancer. Dr. Bob strongly believes Celebrex can help to control prostate cancer cells that are local and/or systemic.

Importantly, there were not any changes in serum testosterone levels in these studies described in this Dr. Bob Celebrex paper. Therefore, the benefit of Celebrex was not due to hormone blockade. These results reinforce my belief that Celebrex may help to control disease progression, and thus may avoid or delay the need to start hormone blockade.

Long before the anti-cancer benefits against prostate cancer or malignant melanoma were known, COX-2 inhibitors had been shown to reduce the risk to develop colon polyps, and in certain instances, reduce the risk to develop colon cancer. COX-2 inhibitors may also have beneficial effects in breast cancer, lung cancer, and other malignancies.

All medicines have side effects. COX-2 inhibitors may adversely affect kidney function. Celebrex contains a type of sulfa and can cause skin rashes, especially for those who are allergic to sulfa, although the form of sulfa in Celebrex is the type found in Lasix (furosemide), and most patients allergic to sulfa do not develop a rash from Celebrex. An occasional patient reports diarrhea; some may develop fluid retention or mildly elevated blood pressure. Liver and kidney blood tests must be monitored while on Celebrex. It is generally agreed that the risk of gastrointestinal bleeding is lower for patients treated with a COX-2 inhibitor compared to patients treated with aspirin or traditional NSAID's, e.g., Motrin, Aleve, ibuprofen, Advil, etc., and all of the medicines in the NSAID drug class. COX-2 inhibitors may have other side

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effects, and you should discuss this subject with your physician. Each patient must consider the risks, benefits, and alternatives for taking any medication.

In all of my prior versions of this paper, dating back to 2001, I warned of the possibility that COX-2 inhibitors could cause increased cardiovascular toxicity. In 2001, I stated that "taking one baby aspirin with food per day while on a COX-2 inhibitor **might** be able to reduce the risk of cardiovascular side effects." This remains an unproven belief, but I believe that patients should strongly consider taking one baby-strength Ecotrin per day (with food) if they are taking Celebrex. Patients on an anticoagulant should check with us so we can review your individual situation to determine whether it is safe to take aspirin while you are also taking an anticoagulant. If you do not have a significantly increased cardiovascular risk profile, Compassionate Oncology feels that most prostate cancer patients should consider taking Celebrex.

In the past, I wrote that anti-cancer benefits were only seen with doses of 400 mg of Celebrex per day. However, there are some intriguing hints that if a patient is taking a statin-type medication (in one study, it was Lipitor) every day, there may be some Celebrex anti-cancer benefit using 200 mg of Celebrex per day rather than 400 mg. This issue is not resolved. What is known is a number of studies have reported that doses of Celebrex of 200 mg per day or less were not associated with any increased risk of cardiovascular complications compared to placebo.

Dr. Bob and Compassionate Oncology Medical Group recommend that each patient assess the risk-benefit ratio regarding the use of Celebrex, and then make an informed decision. We cannot advise a patient to take Celebrex; we can only present all of the available relevant information to them, but the final decision must be made by each person. To date, Celebrex is the only nonsteroidal anti-inflammatory drug that has been shown to have a beneficial effect for controlling PSA's in patients who have prostate cancer.

On December 21, 2004, The National Institutes of Health reported interim results from a trial involving approximately 2,400 patients. These patients had been randomized to receive Celebrex, 200 mg twice each day, naproxen (Aleve is an over-the-counter version of naproxen), at a dosage of 220 mg twice each day, or placebo. Neither the doctor nor the patient knew

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which drug they were taking. All three medications appeared identical. Naproxen first became commercially available in the United States in 1976. It is a nonselective COX-1 and COX-2 inhibitor. The startling results from this study found that patients taking Naproxen had a 50% **higher** risk for cardiovascular events **compared** to patients taking either Celebrex or placebo. Patients randomized to Celebrex had essentially the same number of cardiovascular events as those patients treated with placebo.

Prior to the results of the Naprosyn/Celebrex/placebo study, physicians believed that all of the nonselective NSAID's were cardioprotective. It was thought that the same mechanism that increased the risk for bleeding with the use of nonselective NSAID's also reduced the risks for developing clots in the coronary arteries and/or carotid arteries. That belief was disproved with the findings showing that use of Naprosyn (naproxen) was associated with a statistically significant increased risk of cardiovascular complications compared to Celebrex or placebo.

Additional studies confirm that the use of most NSAID's is associated with an increased risk of cardiovascular complications. Therefore, this problem is not limited to Celebrex or selective COX-2 inhibitors, but also occurs with almost all COX-1/COX-2 nonselective inhibitors.

There is a definite increased risk of cardiovascular complications associated with the use of anti-inflammatory drugs. Initially, most people concluded that this increased risk was limited to the selective COX-2 inhibitors: Vioxx, Bextra (both pulled from the market), and Celebrex. But as reported in *JAMA* on October 4, 2006, Volume 296, Number 13, pages 1633-1644, by author McGettigan, Patricia, et al., an article undertook a systematic review and meta-analysis of controlled observational studies to compare the risks of serious cardiovascular events with individual NSAID's and COX-2 inhibitors. The authors referenced a study in the *British Medical Journal*, 2006; 332: 1302-1305, by Kearney, P.M., et al., which was a meta-analysis of randomized trials, and concluded that high doses of ibuprofen (also known as Advil, Nuprin, Motrin, etc.) and diclofenac (Voltaren is one of the trade names of this generic name) are associated with an increased risk of myocardial infarction. (Diclofenac is actually the most widely prescribed NSAID in the world.) In the United States, our FDA requires that both selective COX-2

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inhibitors, as well as all NSAID's, carry a warning highlighting the potential for an increased risk of cardiovascular events. Interestingly, in contrast, the European Medicines Agency requires labeling of selective COX-2 inhibitors, but has not yet made a recommendation about the cardiovascular safety of the older NSAID's.

The October 2006 JAMA article summarizes the estimates of the relative risk (RR) associated with the use of various COX-2 inhibitors and NSAID's. The use of Vioxx was associated with a relative risk for cardiovascular events of 1.31 for one type of study (case control studies), and 1.53 for another type of study (cohort studies). Combining across all studies, the summary RR was 1.35. This means that patients who take Vioxx have a 1.35 greater risk for cardiovascular complications than patients who do not take this COX-2 inhibitor or an NSAID. A dose effect was apparent with a higher RR with doses in excess of 25 mg per day.

There were eight case control and three cohort studies reported on Celebrex. Celebrex exposure **did not** lead to an elevation of the risk of cardiovascular events with a summary RR of 1.01, and combining all studies, the summary RR confidence interval was 0.91-1.23. This means that the use of Celebrex could be associated with as low as a 0.91 relative risk, or as high as a 1.23 relative risk. When the relative risk has numbers below 1 and above 1, it means that the study was unable to find a significant benefit or risk with the use of that product. There were three studies involving the use of meloxicam (Mobic) with an elevation in vascular risk with a summary RR of 1.25. Sixteen studies reported on ibuprofen and/or Naprosyn individually; nine on diclofenac; six on indomethacin (Indocin), and four on piroxicam (Feldene). The summary RR with Naprosyn was close to 1 at 0.97. Diclofenac and Indocin were associated with an increased risk of cardiovascular events. Summary RR for diclofenac was 1.4, and for Indocin 1.3. Compared with any nonselective NSAID, the summary RR for Vioxx was 1.21, and for Celebrex 0.95. With Naprosyn as the reference, the summary RR for Celebrex was 0.94.

In the comments section of the study, the authors report that in doses of around 200 mg per day, Celebrex **was not** associated with any increased cardiovascular complication risks, but the data did not exclude an increased risk with higher doses. Use of Naprosyn was not associated with any reduction in risk as was suggested by the authors of another report comparing

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Naprosyn to Vioxx. Of the other nonselective NSAID's, the highest risk was seen with diclofenac. This study did not find an elevated RR with ibuprofen, although one of the other studies I quoted did identify an increased risk. The conclusion goes on to state that "at doses of 200 mg or less, there is **no** convincing evidence of an increased risk of cardiovascular events with Celebrex. However, based on randomized data, Celebrex in doses of 400 mg or more is probably associated with some increased risk."

It is fascinating that the controversy that accompanied the discovery that the use of Vioxx caused an increased risk of cardiovascular complications resulted in the discovery of heretofore unknown cardiovascular toxic effects from traditional nonsteroidal anti-inflammatories that have been used for more than 30 years. Initially, as the Vioxx data became well known, it seemed that there was a class effect limited to selective COX-2 inhibitors, and that any and all of them were associated with a substantial increased risk of cardiovascular complications. At the same time, it was felt that using traditional nonselective COX-1 and COX-2 inhibitors was associated with a reduced risk of cardiovascular complications. However, that belief had never been tested. For the first time, it became important to determine with certainty whether the nonselective NSAID's were associated with an increased or decreased risk of cardiovascular problems. I believe almost everyone has been surprised finding that almost all of the NSAID's are associated with an increased risk of cardiovascular complications with many, if not most of them, having a higher risk than Celebrex. Having reviewed a number of additional medical articles, I believe that of all the nonselective NSAID's, Naprosyn is probably associated with the lowest risk of cardiovascular complications. The finding from the October 2006 JAMA article, which found no increased risk with the use of Celebrex in doses up to 200 mg per day, was certainly a very pleasant surprise for me. This should give patients some degree of confidence if they are considering whether or not to use Celebrex.

I hope that the reader can now feel much better prepared and knowledgeable as he/she makes their informed decision regarding the risks, benefits, and alternatives for using Celebrex for its potential anti-cancer benefit. Remember that Celebrex is not FDA approved to treat any type of cancer, other than the familial adenosis polyposis syndrome, which is a condition in which patients develop hundreds of colon polyps, and there is

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essentially a 100% probability for developing colon cancer. Celebrex has been shown to reduce the risk of polyp formation in that condition. The use of Celebrex to try to help any other cancer is considered an off-label indication. I hope that the reader has enjoyed reading about some of the apparent anti-cancer benefits associated with the use of Celebrex. To Dr. Bob, it is obvious that Celebrex has some unique properties and benefits that at least in occasional patients result in spectacular and meaningful clinical responses that have dramatically improved the quality of life for these patients, and may have also prolonged their survival. And for prostate cancer patients, there are a number of studies that have shown that more than 90% of patients treated with Celebrex had a favorable effect on their PSA doubling time. More than 90%; I love that percent, which means that instead of an occasional patient benefitting, we see that in this kind of setting, almost all patients treated with Celebrex had a positive PSA response.

As always --

Be happy,

Be well,

Live long and prosper,

DR. BOB

P.S. Grandchild number eight is due in April.

****** None of the above should be construed as medical advice or consultation, and anything discussed in this paper is meant for information only. All medical treatments, consultations, decisions and recommendations can only be made by the patient and his/her treating physician.

Revised 2/28/07